Toward a Pathophysiology of Attention-Deficit/Hyperactivity Disorder

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Summary: Converging insights into attention-deficit/hyperactivity disorder (ADHD) support the notion that ADHD is best characterized behaviorally as a disorder of self-regulation or executive functioning. Anatomic neuroimaging studies suggest that the relevant regulatory circuits include the prefrontal cortex and the basal ganglia, which are modulated by dopaminergic innervation from the midbrain and by stimulant medications. The emerging model proposed in this review encompasses a developmental perspective into this common condition.

Introduction

In an abbreviated recapitulation of the hold of Galen's teachings on western medicine throughout the Middle Ages, psychoanalytic theories held sway in psychiatry for half a century despite the nearly complete absence of empirical verification. Three major influences have contributed to a revolution in psychiatric perspectives beginning with the birth of clinical neuroscience and neuropharmacology in the 1960s. The 1980 publication of DSM-III[1] codified the shift toward an atheoretical syndrome-based diagnostic system that has accelerated psychiatric research by providing criteria for reliable diagnoses. Coincidentally, the availability of neuroimaging techniques has allowed practical access to the living human brain for the first time, producing a critical mass of researchers and clinicians. Accordingly, it is now feasible to begin proposing theoretical, albeit heuristic, models of psychiatric disorders. Such primitive models are demonstrably "false" in that they necessarily gloss over almost all of the immense complexity of the brain. However, proposing such models can be useful if they lead to specific testable predictions. Only by proposing and rejecting explicit and falsifiable theories can the momentum toward a scientific understanding of normal and abnormal brain function be continued.

This review is an attempt to formulate a schematic model of attention-deficit/hyperactivity disorder (ADHD) based on clinical and basic science observations. The scope of this model is limited to central dopaminergic systems and their regulation of prefrontal circuits, although there is substantial evidence that other systems (especially noradrenergic and adrenergic) are also involved.

ADHD is the most common psychiatric condition affecting children, estimates of prevalence in childhood ranging from 5–10%.[2] The specific definition of ADHD has been modified three times in 14 years by the American Psychiatric Association,[1,3,4] and the diagnosis must still be made exclusively by history, for no laboratory or psychological test or battery is available that provides sufficient sensitivity and specificity. However, there is increasing agreement that ADHD represents a "real" condition, not merely an artifact of unreasonable expectations and crowded classrooms,[5-8] although such agreement is far from unanimous.[9,10]

The most recent revision of the diagnosis of ADHD in DSM-IV includes separate diagnostic criteria for symptoms of inattention and hyperactivity/impulsivity.

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Thus ADHD is now diagnosable as three subtypes: predominantly inattentive, predominantly hyperactive/impulsive, or combined type.[11] This differentiation of two distinct symptom clusters or dimensions represents a clear improvement over the DSM-III-R definition of ADHD, which combined symptoms of inattention, hyperactivity, and impulsivity.[3]

Although estimates of the prevalence of ADHD vary widely, the diagnosis and treatment of ADHD with stimulants, principally methylphenidate, has risen dramatically from 1988 to 1995, as monitored by the Drug Enforcement Administration. Although the increase seems to be ascribable to increases in numbers of prescriptions written rather than to illegal diversion, it has been widely quoted in the lay press as cause for alarm.[10] The most vocal proponents of stimulant treatment for ADHD have been the parents of children with ADHD, but their arguments have been weakened by the imputation of self-interest and by the absence of a coherent explanation for the therapeutic utility of psychostimulants and an understanding of their limitations.

Attempts at understanding ADHD have generally begun with the efficacy of stimulants in reversing many ADHD symptoms for short periods of time.[12-16] Since stimulants typically produce motor hyperactivity in laboratory animals, animal models were sought in which the stimulant effects could be characterized as "paradoxical."[17] The demonstration that dextroamphetamine had similar qualitative effects in healthy children and adults as in children with ADHD[18,19] emphasized the point that psychiatric disorders are not easily modeled in nonhuman species. Thus, despite some interesting partial models,[20-26] the field has not pursued this line of work with much vigor. Rather, most studies over the past two decades have sought to better characterize ADHD in humans, primarily in children. Based on an admittedly selective reading of this voluminous literature, the following conclusions can be extracted.

- ADHD is a common although heterogeneous condition. One element in its heterogeneity is the frequent co-occurrence of other conditions (comorbidity).
- "Pure" ADHD may be best characterized as a risk factor for other psychiatric and psychosocial morbidity such as oppositional defiant disorder, conduct disorder, and substance abuse. Pure ADHD has some negative prognostic import, but this is magnified exponentially by the presence of other comorbid conditions.
- ADHD is a developmentally sensitive disorder, representing at least in part a "neurodevelopmental lag." Impairment associated with ADHD symptoms can continue throughout life, although the specific symptoms and the spheres of functioning that they affect often change. The risk of serious morbidity from ADHD and associated conditions is highest during adolescence.
- Neither specific deficits in attention nor in motor control are adequate to explain the range and variety of ADHD symptoms.
- The psychological construct of "executive functions" provides a useful unifying framework from which to describe ADHD symptoms throughout life.
- The brain circuits that subserve executive functions include the prefrontal cortex, the basal ganglia, and the cerebellum. These circuits are modulated by monoamine neurotransmitters, principally dopamine, which affect the "signal-to-noise" ratio of neuronal communications.
- Modeling ADHD requires an understanding of normal brain development, the most dramatic feature of which is a relative increase in the influence of inhibitory to excitatory effects beginning at toddlerhood. This is paralleled by decreases in brain dopamine concentrations.
- Dopamine metabolite concentrations in cerebrospinal fluid are greatest in the most hyperactive ADHD boys, consistent with findings of a "neurodevelopmental lag."
- Prefrontal circuits, particularly in the right hemisphere, have been implicated by neuroimaging studies in ADHD.
- Delayed maturation of prefrontal circuits into the third decade of life is consistent with the improving prognosis for adults with ADHD.
- Treatment strategies in ADHD must be grounded in a developmental perspective.

Heterogeneity

As noted above, estimates of the prevalence of ADHD can vary from 2% to 18% of school age children.[2,27] This broad range reflects differences in methodology as well as the heterogeneity of the underlying condition. This heterogeneity can be observed within the same family[28] or within the same individual. For example, I evaluated a 15-year-old female who had been noted to be well above average in both hyperactivity and intelligence during her elementary school years although

she did not display any obvious deficits in attention. By the time her distractibility, disorganization, and forgetfulness became impairing in middle school, her obvious motor symptoms had diminished. Academic and social failure had contributed to depression and anxiety, for which she was unsuccessfully treated for nearly 2 years with intensive psychotherapy and antidepressants. Detecting the subtle but clear evidence of ADHD in her past and present functioning allowed her to benefit pharmacologically from the addition of a stimulant to her antidepressant, and psychotherapeutically as a result of increased self-awareness. It also resulted in the discovery that the adolescent patient's mother had experienced similar symptoms for her entire life, for which she had coped as an adult by repeatedly refusing job promotions.

Another type of heterogeneity that needs to be considered whenever the diagnosis of ADHD enters a differential diagnosis is attributable to comorbidity. Approximately one quarter of children with ADHD also have specific learning disorders in reading, math, and written or spoken language, although estimates range from 6% to 92% in referred samples.[29,30] Current practice is to diagnose and treat each disorder independently. However, there is at least one interesting report that distinguished children with ADHD alone from those who had ADHD as well as reading disorder (dyslexia). The authors concluded that the latter group did not have the same neuropsychological deficits as the pure ADHD group, suggesting that distractibility and inattention in the classroom had developed as a consequence of a primary disability in learning how to read.[31]

Developmental Course of ADHD

As a disorder identified primarily with pediatric patients, it is not surprising that ADHD raises several developmental issues. First, a number of observations support the conclusion that ADHD represents at least in part a "neurodevelopmental lag."[32] For example, children with ADHD trail about 2 years behind age-peers in social development, as measured by the Vineland Scale.[33] A similar gap of 2–3 years was found in cognitive tests believed to tap prefrontal functions in 8- to 9-year-olds, and in 10- to 12-year-olds.[34,35] Thus both controls and ADHD patients seemed to be progressing at the same rate but with a relatively constant lag. Second, the symptoms of ADHD change over time. The most salient characteristic of the young child with ADHD is motor hyperactivity, which decreases over time independent of treatment.[36,37] By contrast, symptoms of inattention show little regression over time.[37] In fact, it is not uncommon for symptoms of inattention to be difficult to discern in the elementary grades, only to become more manifest as the complexity of academic challenges increases.

A third developmental issue concerns the natural history of the disorder which can be accurately described only by using longitudinal follow-up studies. Mannuzza and Klein performed the most rigorous study of this genre by following nearly 100 subjects for more than 2 decades, along with a socioeconomically matched control group.[38] Their group found that 52% of the subjects who continued to display ADHD in adolescence met criteria for substance abuse or criminal behavior.[39] Fortunately, when subjects were interviewed in their 20s, the percentage who met criteria for antisocial personality disorder had decreased from 25% to 15%.[38] These results are consistent with other findings that adolescents with ADHD are at a much increased risk for alcohol and substance abuse[40-43] and that they are more likely to be involved in motor vehicle accidents.[44,45] The risk of substance abuse is particularly high when ADHD is combined with aggression or conduct disorder,[46] even when detected in early childhood.[47,48] Interestingly, 18% of subjects in the Mannuzza and Klein study owned small businesses versus 5% of controls,[38] leading to speculation regarding the potential benefits of high levels of activity and willingness to take risks for entrepreneurship.

Executive Functions and the Neuropsychology of ADHD

While the potential utility of ADHD-related traits in some adult endeavors is intriguing but unproven, ADHD rarely offers much benefit during academic pursuits. Neuropsychological approaches have been employed in an attempt to isolate the cognitive deficit or deficits underlying ADHD so as to improve diagnosis and implement more targeted treatments.

Early neuropsychological studies in ADHD were shaped by the demonstration that stimulants robustly improved performance on the continuous performance test (CPT).[49] The classic CPT primarily measures vigilance, defined as the ability to respond appropriately to a rare stimulus. While the studies reporting group differences on vigilance tasks in ADHD are too numerous to cite,

not all patients with ADHD display deficits in vigilance or in other measures of attention.[50]

The search for neuropsychological deficits that would correspond to the symptoms of ADHD has come to focus on the concept of executive function,[51] which in turn has derived from clinical investigations of patients with lesions affecting prefrontal circuitry.[52,53] Executive functions have been defined as "control processes . . . [involving] inhibition and delay of responding [allowing an individual to] initiate, sustain, inhibit/stop, and shift."[53] Also associated with the construct of executive function are the abilities to prioritize, organize, and strategize.[52] The concept of executive *dysfunction* captures the patient who has ADHD, who as noted in the title of a popular book, has difficulty "Putting on the Brakes."[54] The similarities between patients with ADHD and those who have gross lesions of prefrontal brain have long been noted, but so too have the limitations of this crude comparison.[55-58] Over the past decade, however, a more nuanced understanding of the subcortical circuits that subserve frontal functioning has emerged, catalyzed by the work of Alexander and colleagues.[59,60]

Prefrontal Circuits

In 1986, Alexander et al pointed out that a number of discrete somatotopically distributed circuits could be delineated connecting prefrontal afferents to basal ganglia relay stations, which then synapse at thalamic nuclei, which in turn feedback to the cortex.[59] This cortical-striatal-thalamic-cortical circuit provides both positive and negative feedback to other cortical regions and is believed to serve as the anatomic substrate for many of the executive functions. In the decade since, this circuit has been the object of intense study in rodents, nonhuman primates, and humans.[61-64] It is still far from completely understood, but it is now possible to draw simplified circuit diagrams that can at the very least lead to testable predictions. Such an admittedly simplistic diagram is shown as Figure 1. The elegant complexity of the prefrontal cortex is schematized as a single rectangular box, with excitatory outputs to the caudate nucleus and to a small but key structure known as the subthalamic nucleus (STN).[65-68] Neuronal signals that travel from the caudate *directly* to the medial globus pallidus (also known as the internal segment of the globus pallidus and abbreviated GP_i) result in a net amplification via disinhibition of thalamic excitatory fibers, which feedback to the original cortical output neuron or to other cortical regions. The so-called *indirect*

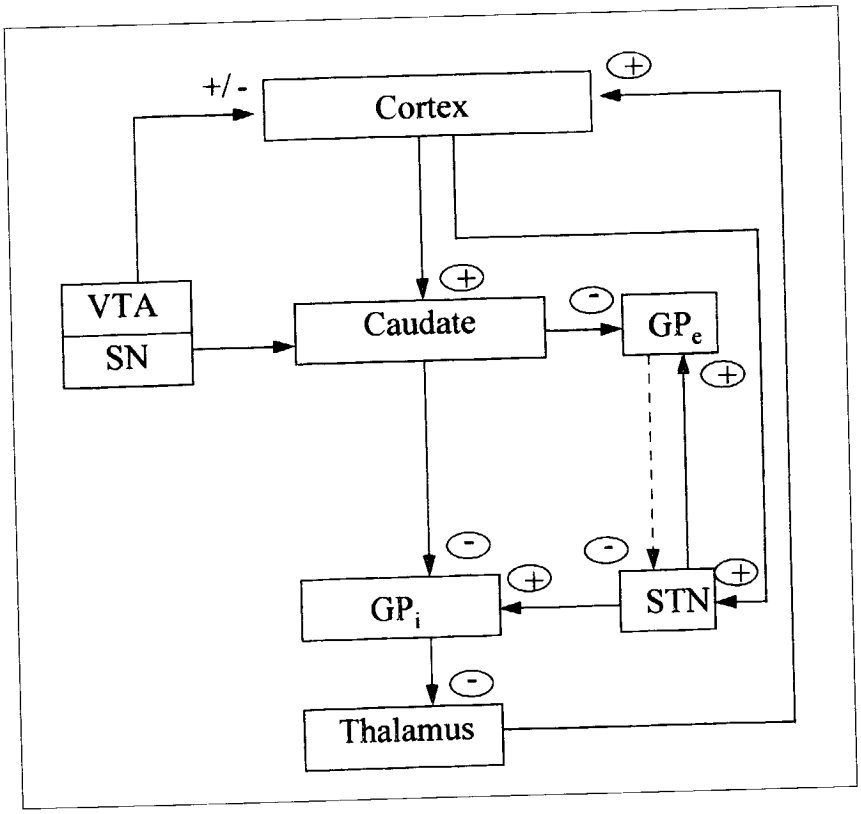

Figure 1. Schematic of a prefrontal-striatal-thalamic-cortical circuit. Abbreviations: VTA = ventral tegmental area; SN = substantia nigra; GP_e = globus pallidus external segment, also known as lateral GP; GP_i = internal segment or medial GP; STN = subthalamic nucleus. Efferents from the cortex, subthalamic nucleus, and thalamus are all excitatory (glutamate). Efferents from the caudate and from both globus pallidus segments are inhibitory (GABA). The net effect of dopamine released from the substantia nigra via the nigral-striatal circuit is to increase the positive feedback from the thalamus to the cortex through either the direct pathway (caudate to GP_i) or via the indirect pathway (which includes the GP_e and STN). Dopamine released from the VTA to the cortex affects signal-to-noise of other cortical inputs. This schematic differs from prior versions in deemphasizing the flow from the GP_e to the STN (personal communication, Dr. D. Kreiss, September 1996).

pathway includes the lateral globus pallidus (or external GP, thus GP_e) and the STN. Neuronal traffic through this pathway results in further increases in the tonic level of inhibition produced by this system. This can be said to be the brain's braking mechanism.[69] Inadequate inhibitory tone in the indirect pathway, or excessive activation via the direct pathway, has been posited for a number of psychiatric disorders, including ADHD, Tourette's disorder, and obsessive compulsive disorder.[70-73] This lack of specificity is not altogether surprising, since the combination of these three disorders is not rare. The factors that determine whether one, two, or all three disorders will manifest in a given individual are not yet known, although it is believed that the monoamines, particularly dopamine and serotonin, are involved. The links among the monoamines are important and complex but still poorly understood. Although this review focuses exclusively on the dopamine system, there is also a great deal of evidence for a role of noradrenergic and adrenergic influences in ADHD.[16,74]

Stimulants and Dopamine Terminals

After synaptic release, dopamine, like all monoamines, is primarily deactivated by reuptake into the presynaptic terminal via a specific transporter, not surprisingly called the dopamine transporter (DAT).[75] Once inside the terminal, monoamines are repackaged into synaptic vesicles through a nonspecific monoamine vesicular transporter. Methylphenidate blocks the dopamine and norepinephrine transporters, whereas amphetamines block the vesicular transporter, thus affecting not only dopamine and norepinephrine but also serotonin. The net immediate effect of either type of stimulant is an increase in the synaptic concentration of monoamines, which produces an increased postsynaptic effect. However, monoaminergic circuits are tightly regulated, both by long-distance feedback and local feedback from inhibitory dopamine receptors located in the presynaptic nerve terminal. These *autoreceptors* can rapidly regulate the level of synaptic neurotransmitter release. The net effect of a particular dose of a given stimulant is a complex function of multiple elements, including pharmacokinetic factors.[76,77]

Dopamine and the Cortical-Striatal-Thalamic-Cortical Circuit

The most convincing evidence for the importance of dopamine in normal functioning within prefrontal-basal ganglia circuitry comes from Parkinson's disease, in which symptoms of tremor, akinesia, and rigidity emerge after the death of the majority of dopaminergic neurons in the substantia nigra (SN in Figure 1).[69] Reversal of this dopaminergic deficit, by the administration of levodopa or of dopaminergic agonists, relieves symptoms, provided a few dopaminergic terminals remain, but relapse has generally been inexorable. As depicted in Figure 1, the deficit in dopamine results in excessive inhibition through the indirect pathway, motivating a return to neurosurgical ablation of neurons in posterior-lateral medial globus pallidus for patients with end-stage Parkinson's.[78-81] These neurosurgical studies are also obtaining unique data regarding basal ganglia electrophysiology that will further elucidate these intricate circuits.[82,83]

Dopaminergic influence extends beyond motor control, as concluded by Schultz and colleagues on the basis of electrophysiologic studies in primates.[84] They found that some "dopamine neurons and neurons in the ventral striatum only respond to reward when it is not entirely predictable, such as during the trial-and-error learning of tasks with specific constraints and during self-initiated movements without preceding reward-predicting stimuli. . . . It appears . . . that the response is due to the salient, alerting stimulus property of primary reward during learning."[84,85] Salience and reward are often confounded, but when they are experimentally dissociated, it is salience that is dopaminergically based.[86-88]

While the dopamine cells in the substantia nigra innervate primarily the striatum, the ventral tegmental area (VTA in Figure 1) contains dopaminergic cells that diffusely innervate the frontal cortex, terminating primarily on dendritic spines of cortex pyramidal cells.[89] Work in primates suggests that dopamine is involved in "direct gating of selective excitatory synaptic inputs to prefrontal neurons during cognition."[90,91] In an elegant demonstration of these effects in normal humans, volunteers underwent blood flow measurements with positron-emission tomography after double-blind placebo and dextroamphetamine while they performed two distinct tasks. In both cases, amphetamine increased the signal-to-noise ratio of cortical activation, with increases in those regions previously found to be

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activated by the specific task, and decreases in other uninvolved regions.[92] It is of particular interest that VTA neurons in human and primate, unlike those that emanate from the substantia nigra, lack autoreceptors,[93] which explains why the prefrontal dopaminergic system is much less susceptible than the striatum to up- or down-regulation of dopamine receptors by dopaminergic agonists or antagonists.[94-97] It seems reasonable to conclude that it is the lack of susceptibility of this circuit to tolerance that provides the basis for long-term stimulant treatment.[98]

Dopamine and Development

The proposition that motor hyperactivity in children with ADHD represents a type of reverse Parkinson's is clearly simplistic. However, several lines of evidence make this possibility worth considering. Of the three monoamines (dopamine, norepinephrine, serotonin), dopamine is the most developmentally active. Dopamine metabolite concentrations in cerebrospinal fluid (CSF) peak at about age 2 and decline fairly rapidly over the next dozen years.[99] Brain blood flow and metabolism also decline during this age range,[100] and so does the overall level of motor activity. Activity levels of normal children have not been compared to CSF dopamine metabolites, but the supposition that the two are positively correlated has been supported in studies carried out in adults[101,102] and in animals.[103] It seems fortuitous that young children would be supplied with a surfeit of the particular monoamine neurotransmitter that facilitates exploration of their environment and that the concentrations of this substance would generally decrease as they become older and less adventurous.

Dopamine and ADHD

Attempts to characterize monoamines in ADHD have been frustrating because of the large peripheral contribution in blood and urine. Concentrations of the principal dopamine metabolite, homovanillic acid (HVA), in CSF are more reflective of central dopamine function, although it is not possible to pinpoint the source of differences in metabolite levels. At the NIMH, my colleagues and I were initially surprised to find that CSF HVA concentrations were significantly and positively correlated with the degree of hyperactivity in 29 boys.[104] We found the same significant correlation in an independent sample, and we also found that the CSF HVA concentration obtained during a drug-free baseline level in the combined sample (n=45) was the best predictor, after baseline symptom severity, of therapeutic response to methylphenidate, dextroamphetamine, or pemoline.[105] With all three drugs, the boys with the greatest CSF HVA concentrations had the best responses to treatment. These results were consistent with an earlier study that documented postamphetamine decreases in CSF HVA that were highly correlated with behavioral improvement.[106] Combined with the assumption (based on the animal literature[107]) that most CSF HVA originates in the striatum, our results suggest that motor hyperactivity is associated with larger concentrations of HVA in the caudate, as would be found in a neurologically younger child. Our data are also consistent with the conclusion that stimulant treatment is associated with a decrease in CSF HVA, presumably through decreases in dopamine release from the substantia nigra. However, even if we were to conclusively demonstrate this relationship, the inherently nonlocalizing nature of CSF studies means that we could not distinguish between a true effect and epiphenomenon. De-confounding these results at the molecular level will require advances in our understanding of the genetics of ADHD.

Genetics of Dopamine and ADHD

Specific molecular abnormalities have been proposed in ADHD in the dopamine transporter,[108] and in the D4 dopamine receptor subtype.[109] The dopamine transporter report was especially interesting because a mouse knockout of the same gene displays extreme hyperactivity.[110] However, this finding was not replicated by another group,[109] although they did find that the same D4 dopamine receptor allele that had been associated with novelty seeking in adults[111,112] was significantly associated with ADHD. Pending ongoing attempts by several groups to replicate this report, it is premature to speculate on the mechanisms of these putative genotypes, except to note that D4 dopamine receptors are abundant in globus pallidus and in GABAergic interneurons in prefrontal cortex.[113]

Neuroimaging in ADHD

The other source of evidence that supports a role for the basal

ganglia inhibitory circuits in ADHD comes from brain-imaging studies. While important methodological issues have not yet been fully worked out, there is an increasing convergence of results demonstrating both structural and functional brain differences in patients with ADHD. The most well known have been studies that used [^{18}F]fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography (PET) to demonstrate decreased frontal cerebral metabolism in adults with ADHD.[114] Subsequent work also detected increases in right caudate metabolism after amphetamine under some conditions,[115] although inconsistent results in adolescents[116,117] have led the authors to explore other techniques in ADHD. Other investigators of brain function have measured local cerebral blood flow, which closely approximates neuronal activity, with a variety of techniques including ^{133}Xenon inhalation and single photon emission tomography (SPECT). Decreased blood flow has been found in ADHD subjects in the striatum,[118] and in prefrontal regions.[119] However, these results remain tentative because ethical constraints make it difficult to obtain truly independent observations from normal controls. A more promising technique may be blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (FMRI), which obviates the need to use ionizing radiation. A preliminary report using this new technology has once again shown hypoperfusion in the right caudate, which reversed on optimal dose methylphenidate treatment.[120]

Our own group has concentrated on using anatomic MRI to discern structural brain differences in 57 boys with ADHD compared with 55 controls.[121] We found that the normal boys had a significant asymmetry of the caudate, the right side being 3% larger than the left on average. In contrast, the ADHD subjects demonstrated no asymmetry as a group, and the degree of loss of asymmetry correlated with their performance on tests of response inhibition.[122] We also found that the right prefrontal brain region was significantly smaller in the ADHD boys, while the left side did not differ from controls. The globus pallidus was also significantly smaller, particularly on the right. In addition, the volume of the cerebellum was significantly smaller in ADHD, and there were significant differences in the increase in ventricular volume over time, which was consistent with a delay in maturational changes in the boys with ADHD. Other groups have also found differences in caudate[123,124] and globus pallidus,[125] although the side of the greatest difference has not always been consistent. There have also been a number of reports of abnormalities in the corpus callosum area,[126-129] although again the specific regions have not always been concordant from one study to another. Taken as a whole, however, the brain-imaging studies lend substantial support for the prediction enunciated in 1991 by Heilman and colleagues that right-sided abnormalities of the prefrontal-basal ganglia circuit would be found in ADHD.[130] Not all basal ganglia structures are apparently implicated, however; the putamen, which receives inputs from primary motor cortex, has not been found to differ in ADHD. This again supports the linking of ADHD and prefrontal circuits that subserve executive functions.

Hemispheric Lateralization and ADHD

The prefrontal-striatal circuit is bilateral, but neurologic observations in patients with neglect syndromes suggest that the right hemisphere may be "dominant" in spatial awareness and in directing attention.[131-133] Many, though not all, of the unilateral findings from neuroimaging studies in ADHD point to the right frontal-basal ganglia circuit. Phenomenologically, subtle but significant laterality differences have been extensively noted in ADHD, suggesting greater dysfunction in the right hemisphere.[134-143] It has been suggested that left-sided anatomic differences in ADHD may be the result of a higher rate of comorbidity for verbal learning disorders in that sample.[125]

A Tentative Pathophysiology of ADHD and Its Implications

Models of ADHD that have proposed a hypodopaminergic state resulting in hypofunction of the prefrontal circuitry have assumed a unitary dopamine system. The present hypothesis takes advantage of the major differences between the two pertinent dopamine systems. Dopamine neurons originating in the VTA diffusely innervate frontal cortex, forming the *mesocortical dopamine system*, which largely lacks inhibitory autoreceptors. These dopaminergic terminals are ideally positioned to regulate cortical inputs, thus improving the signal-to-noise ratio for biologically valued signals. In this circuit, therapeutic doses of stimulants are hypothesized to increase postsy-

naptic dopaminergic effects and promote the integration of relevant inputs from other cortical regions, thus enhancing executive functions. Because this circuit does not have the cellular machinery required for tolerance, relatively constant effects can be obtained over months or even years.

By contrast, symptoms of hyperactivity/impulsivity in children with ADHD are hypothesized to be associated with relative overactivity of the dopamine circuit, which extends from the substantia nigra to the striatum. This *nigral-striatal circuit* is tightly regulated by inhibitory autoreceptors as well as by long-distance feedback from the cortex, and slow diffusion of therapeutic doses of stimulants via oral administration is hypothesized to produce a net inhibition of dopaminergic neurotransmission. However, this therapeutic down-regulation can be overwhelmed if a stimulant is delivered by intravenous or intranasal routes or by rapid increases in dose. Such nontherapeutic usage patterns are required to produce stimulant abuse and dependence. This explains why stimulant treatment of cocaine addicts who are comorbid for ADHD with stimulants can be effective,[144,145] and why therapeutic use of stimulants has not been implicated as a risk factor for substance abuse. This model is consistent with the therapeutic utility of very low doses of methylphenidate[146] and with the observation that the severity of "rebound" hyperactivity is inversely related to the age of the child[147] and to the rate at which stimulant effects decrease. It also predicts that stimulant effects on hyperactivity/impulsivity should demonstrate at least partial tolerance. This observation has been reported anecdotally but has not been rigorously tested. Experiments bearing on this question are currently ongoing (personal communication, Dr. J. Swanson, August 1996).

Conclusion

The attention paid in this review to pharmacologic effects on neuronal circuits should not be interpreted as implying that ADHD is exclusively treatable with medications. As in the case of obsessive-compulsive disorder, where both medications and behavioral treatments affect brain function, behavioral techniques likely evoke similar but even more specifically targeted effects in the brain. Behavior modification schedules increase the salience of socially sanctioned responses, thus increasing the likelihood that specific midbrain dopaminergic neurons will be activated, leading to better control of hyperactivity/impulsivity. At the cortical level, coaching cognitive strategies[148] can assist in the amelioration of executive dysfunction associated with the symptoms of inattention. When behavioral supports are inadequate in either of these dimensions of impairment, as is often the case, stimulant medications are able to provide additional temporary support, albeit by different mechanisms. By facilitating the maintenance of Barkley's "prosthetic environment,"[149] comprehensive treatment of ADHD can minimize the risks of serious morbidity while neurologic maturation of prefrontal self-regulatory circuits proceeds.[150-154]

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